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BACILLUS COLI INFECTIONS

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The BACILLUS COLI is a normal inhabitant of the bowels. In the vast majority of people, its presence is never felt. But in many others these organisms stray from their usual habitat to other parts of the body, in some cases near, and in others far removed from, the colon. They may be found in situations as far away as the brain, producing meningitis, or the lungs, causing pleurisy and sometimes even gangrene. In the abdomen itself, B. COLI may be responsible for such diverse conditions as appendicitis, peritonitis—B. COLI being the most common organism found in this condition—and ulcerative colitis. The liver and particularly the gall-bladder are often infected, producing suppurative cholangitis, cholecystitis, and gallstones. The organism is frequently found in the urine, and is probably the commonest cause of pyelitis and cystitis. In most of these conditions, the symptoms could be readily traced to a particular organ. But sometimes the manifestations are so general that the disease is often mistaken for such conditions as tuberculosis of the lungs or abdomen and typhoid fever. In other words, a true B. COLI septicæmia occurs. It is not possible to deal adequately in one paper with all the disorders that might result from B. COLI infection. The two common and important infections are those of the gall-bladder and the genito-urinary tract. I propose to limit myself to a consideration of B. COLI infection of the genito-urinary tract.

INCIDENCE

B. COLI infection occurs in both sexes and at all ages, though it is much more common among women than men. Similarly, among children, girls are more frequently subject than boys. Pregnant women form by far the largest number of patients. Some authors believe that the infection

chiefly occurs in young women while they are pregnant and that the cases seen for the first time in later life are merely residual infections.

ROUTES OF INFECTION

There can be no doubt that the source of infection is the colon. But opinion is very much divided as to the path taken by the organism to enter the various tissues concerned. Three routes are generally incriminated: (1) from the anus to the urethra and the bladder; (2) from the damaged mucous membrane of the colon to the blood stream and thus to various organs; and (3) from the colon directly to the contiguous kidney. The exact route taken is of very great interest to the experimental pathologist. But it is not altogether a matter of indifference to the physician. It would, therefore, be useful to discuss here briefly the various views in regard to the route.

The urethral route or ascending infection.—The urinary tract is the commonest site of B. COLI infection. The urethral outlet is close to the anus. The infection is far more common in women and girls than in the male, and in the former the urethra is very short. These facts have led some people to believe that the infection travels from the perineum to the urethra and upwards to the kidney *via* the bladder. But there are important reasons which make this theory untenable. In the first place ascending infection is anatomically improbable in the male. And in both sexes it would be unreasonable to presume that the infection can progress "against the current". Where there is both cystitis and pyelitis in the same patient, clinical evidence is overwhelming in favour of the kidney being the earlier site, and cystitis a subsequent complication. And the fact that pyelitis is more easily cured than cystitis lends support to the view that the kidney is involved first. A B. COLI urethritis is clinically unknown. And if such a method of infection were possible, B. COLI infection of the bladder and kidneys should be almost universal in female infants on account of the use of napkins. It is, therefore, difficult to believe that the infection generally occurs by way of the urethra, though it would be impossible to deny that some cases might be so infected. Even in these instances, the infection is far more likely to be by way of the peri-urethral and peri-ureteral lymphatics than along the lumen.

Circulatory route.—Many physicians favour the view that the B. COLI enters the blood stream from the damaged mucous membrane of the colon. People who suffer from this infection are generally badly consti-

pated patients. The chronic stasis in the colon probably produces slight abrasions or other changes in the mucous membrane which allow the organism to enter the blood stream. The order of events which is observed in acute cases ordinarily seen in the medical wards supports this view of infection by the blood route. A first attack of pyelitis is ushered in with general malaise, headache, chillness or severe rigor leading to a temperature which may rise to 103° F. or more and pain in the loin. Frequency of micturition and dysuria set in only some hours later. The aspect of the patient is more suggestive of a general than a local infection. In fact, in many cases the local symptoms are so negligible that physicians are misled in diagnosis. According to this view, B. COLI infections of the urinary tract should be regarded as an "excretion pyelitis" in which a B. COLI bacteriæmia exists first and in which the pyelitis is merely the result of the bacteria being excreted by the kidney. Berrington and Wright have shown that bacteriæmia with or without rigor follows operations on the urethra. This probably explains "catheter fever" which so closely resembles the prodromal stage of a pyelitis.

Transperitoneal route.—Obstetricians concede that the infection sometimes occurs *via* the blood stream. But they believe that in the majority of cases, that is, those which occur during pregnancy, the kidney is infected direct from the colon. The right kidney is far more frequently affected than the left. And it is much closer to the colon. The contents of the ascending colon is more fluid and this fluid state probably helps to keep the B. COLI active and more likely to penetrate the mucosa. These facts are held to favour the theory of direct infection. The infection is said to travel by the lymphatic route, though there is no anatomical basis for the existence of lymphatics connecting the kidney to the colon.

Neither experimental nor clinical evidence is conclusive as to the exact route of infection. It is probable that infection does not follow the same route in all cases, but might select any one of the above routes depending on conditions of which we are perhaps ignorant at present. But the weight of opinion is in favour of the blood route in the majority of cases. The organism having entered the circulation produces certain prodromal symptoms. This phase of bacillæmia is but of short duration—just a few hours—,and very likely the bacillæmia ends where bacilluria begins. When the organisms leave the circulation, they might be completely eliminated, or they settle down in any of the various tissues of the body. What gives character to this particular infection is the preference of B. COLI to colonize

the genito-urinary and biliary tracts after it is eliminated from the circulation. It is difficult to explain this preference. It is analogous to the meningococcus preferring the meninges and the pneumococcus the lungs, though both of them enter the circulation from the upper respiratory tract.

The residual infections which follow colon bacillæmia may involve any of the following organs: the kidneys, the bladder, the gall-bladder and bile ducts, the prostate gland, the testicles; occasionally more than one of these structures are involved at the same time. Whichever part of the body might be the final seat of inflammation, under appropriate treatment the inflammation completely resolves leaving the patient entirely free from the infection. But where the kidney or the gall-bladder is involved the infection does not clear up so well. The patient is often left with a low grade infection without symptoms, or she suffers from vague ill-health with occasional acute recurrences. The more severe initial illness may, however, be followed by complete and lasting recovery.

CLINICAL FEATURES AND COURSE

B. COLI infection of the urinary tract is often silent, that is, the patient might be carrying the infection for months or years without any recognizable symptoms of ill health. At the other end, the disease might set in with such outspoken severity and directness that the site of infection is not long in doubt. Between these extremes there is a large number of patients who are chronic invalids and who are variously suspected to be suffering from tuberculosis, "dyspepsias", or other chronic disorders. While the silent and chronic infections could only be diagnosed after a careful and thorough investigation, the acute cases have often certain definite symptomatology by which they could be generally known. These acute cases begin with more or less malaise and prostration. There is a sharp attack of fever which might go up to 102° F. or more. There may be pain in the abdomen and occasionally some distension. Often there is pain in the loin, more commonly on the right side. There is frequency of micturition with scalding pain at the end of the act. Occasionally there is a transient hæmaturia. Intractable itching at or in the anus was complained of by one of my patients. The urine is loaded with pus cells. With early diagnosis and correct treatment, the temperature comes down rapidly by lysis within a few days. But cases vary in their severity and course. They could be better described by quoting a few illustrative cases.

CASE 1.—The first patient recognized by me as suffering from B. COLI infection was a young woman just two days after the birth of her first child. She had a temperature of about 104° F. which set in with severe rigor. It was suspected that she had malaria. The shivering and pyrexia recurred on the next day. She now complained of a little frequency of micturition and burning pain during the act. She was promptly treated with stock vaccine and almost immediately after the first injection, the shivering stopped, the temperature was reduced, and within three days she was free from fever and symptoms.

CASE 2.—A young lady after her first child-birth. The labour was difficult, and delivery was instrumental and was attended with a badly lacerated vagina and torn perineum. On the third day of the puerperium, she complained of agonizing burning during micturition. There was curiously no frequency. The distress was so great that she dreaded the act of micturition. The urine had to be drawn by catheter twice daily for a few days. The urine was very cloudy and full of pus cells. There was a trace of albumin. There was a slight rise of temperature, but fever was not a prominent feature. She was treated with intravenous injections of urotropine. After the third injection, the urine cleared up and the pain and distress was relieved. She was complaining of a slight burning during micturition during the latter half of her pregnancy. Not much notice was taken of this symptom. She was ordered by the attending physician to take plenty of barley water which used to give her relief. She is now the mother of three children. She has not had any recurrence of the trouble during the last two confinements. But she occasionally experiences a little burning micturition, and she treats herself by taking some barley water for a few days.

CASE 3.—A boy of 8 years was having fever for over three weeks. The temperature was irregular and ranged from 99° to 103° F. It was at first thought to be enteric fever. Abdomen was not distended. There was no enlargement of the spleen and as the temperature was irregular tuberculosis was suspected. But there were no physical signs in the lungs or abdomen. On enquiry it came out that the child complained of slight burning during micturition once or twice during the illness, but this was never a prominent feature. The urine was acid, opalescent, contained plenty of pus cells and a trace of albumin. The child was then put on hexamine by mouth. Within a few days, the temperature touched

normal and the child was well by the end of a week. The urine, however, still showed a few pus cells.

Hale White mentions a case which was known previously to have B. COLI infection of the urine. The patient was suddenly seized with an acute attack which was very strongly suspected to be appendicitis. During the attack the urine showed pus cells, and B. COLI was cultured from it. In spite of this, the high temperature and the general constitutional symptoms were so severe that it was decided to operate at once. A perfectly healthy appendix was removed and the wound healed by first intention. The patient was put on the usual treatment for B. COLI infection and he soon got perfectly well.

Cases are on record where colic due to B. COLI infection was mistaken for that of a stone in the kidney. Sometimes the pain may be right across the loin closely simulating lumbago. In intractable cases of this nature, urine examination would be very useful. Some children complain of fleeting attacks of colicky pain. Repeated examination of the stools reveals no ova and treatment for worms produces no results. Localizing signs are entirely negative. It might be that some of these cases are really B. COLI pyelitis.

DIAGNOSIS

It is not generally difficult to diagnose B. COLI infection of the urinary tract. The most important aid in this, as in many other conditions, is to remember the probability of the existence of this infection as a cause of illness. These cases could be classified into two groups:—

1. Cases with urinary symptoms
2. Cases without marked urinary symptoms.

1. Cases with urinary symptoms are easily diagnosed from the frequency of micturition and pain in the act. The examination of the urine is the most important revealing factor. The difficulty here is not about the question of infection, but to know the nature of infection. Bacteriological examination with cultural methods clinches the diagnosis. But in the absence of such facilities one could generally diagnose B. COLI infection from the following points:

(a) In bacilluria due to B. TYPHOSUS and other organisms urine may not show any pus cells. But in B. COLI infection, pus is constantly present, though the amount might vary from frank pyuria to a few pus cells detected under the microscope.

(b) The urine is generally not clear, but cloudy or slightly opalescent. This opacity takes a long time to settle down to form a deposit. This is said to be a very characteristic feature of B. COLI infection.

(c) When held up to the light the urine shows a "shimmering." If a fresh specimen is available, this shimmering is a very useful sign in the diagnosis of obscure fevers.

(d) The urine is usually always strongly acid, though it may occasionally be alkaline if only cystitis is present.

(e) The urine gives the characteristic "fishy" odour. Often this smell is not present when the urine is passed, but develops after standing for some time. This peculiar smell is specially common in chronic cases.

Apart from knowing the nature of the infection, it is essential to know the seat of infection. The most common conditions that result are pyelitis, cystitis, prostatitis or orchitis. Pain, pyuria and pyrexia are the three important symptoms common to these conditions, but they vary in their severity according to the seat of infection.

Cystitis is not generally associated with notable pyrexia or marked general constitutional symptoms.

If fever is a prominent feature of any case of pyuria or dysuria, it is generally pyelitis or prostatitis. The latter could be diagnosed by local signs of inflammation. Ralph Thomson records a case of chronic pyuria with multiple neuritis. X-rays revealed the presence of multiple stones in the prostate. The removal of the stones resulted in the disappearance of pyuria and the cure of the neuritis.

The diagnosis of orchitis would be obvious, but it might be mistaken for gonorrhoeal or filarial orchitis.

When one is in doubt as to the diagnosis between pyelitis and cystitis, the location of pain is often very helpful. Pain in some degree is constant in both conditions. But in pyelitis, it is in the loin, sometimes very closely simulating lumbago, where, as in cystitis, the pain is often in the hypogastrium.

Cases have been reported where hæmaturia was associated with the urinary symptoms. They have been mistaken for cases of renal calculus. B. COLI pyelitis by itself without any stone is sometimes enough to produce this rather rare type of hæmaturia.

2. Cases without marked urinary symptoms are sometimes the despair of the diagnostician. When the symptoms are severe and the illness acute, these cases might be mistaken for some of the most severe infectious fevers or conditions where inflammation of organs is an important feature. I have already referred to these difficulties while describing the clinical features of the disease. The silent cases may be acute or chronic.

Acute conditions.—Appendicitis, the typhoid group of fevers, and atypical lung and pleural conditions are those that are commonly suspected in obscure cases. A patient suffering from fever and pain in the right side of the abdomen or the lower part of the chest might easily be mistaken for a case of appendicitis or pleurisy, particularly of the diaphragmatic surface, while the actual cause of the trouble might be a right-sided pyelitis. Chronic pyelitis and cholecystitis have often led to the removal of perfectly healthy and innocent appendices.

Continued pyrexia with mild constitutional symptoms, sometimes even severe general symptoms, has often been mistaken for enteric fever, particularly the para-typhoid variety.

Paroxysms of high-peaked pyrexia with convulsive rigors and terminal sweating could easily simulate malaria. When the period of pyrexia is more or less continuous for 36 or 48 hours, filarial fever might be wrongly suspected. But the absence of parasites in the blood and the absence of the characteristic regional inflammation and pain should caution us from a diagnosis of malaria or filarial fever respectively.

During the puerperium, care must be taken not to mistake a B. COLI infection for the far more serious condition of puerperal sepsis.

Chronic B. COLI infections of the gall-bladder or the kidneys produce a state of chronic invalidism. The children are thin, under-nourished and stunted. They suffer from vague symptoms of pain or discomfort in the abdomen and repeated attacks of mild indigestion. When such symptoms are associated with prolonged low fever, or occasional spells of sharp rise of temperature, chronic tuberculous affection of the lung or the peritoneum is generally thought of. And in adults under similar conditions, chronic fibroid tuberculosis of the lung is the usual diagnosis. In some children frequent attacks of colic and inexplicable poor health make one suspect infestation with worms. But repeated examination of stools fails to show evidence of worms, and even after careful treatment, the symptoms persist. Some of these cases are undoubtedly B. COLI infections of the kidney or

gall-bladder. In all these cases diagnosis would be obvious if the history of the case and the evolution of the symptoms are carefully taken and the urine is thoroughly investigated.

PROGNOSIS

Urinary Tract.—It is sometimes difficult to be certain of the course and termination of B. COLI infections. The prognosis has to be cast in regard to (1) life, (3) full restitution of health, and (3) bacilluria. The prognosis in regard to life is uniformly good. But where bacilluria complicates old age or chronic nervous disorders like paraplegia, it certainly hastens the end. When associated with obstruction of the ureters or enlargement of the prostate, it becomes the despair of the surgeon on account of the imminent renal failure. It is not possible to be so certain when it is a question of complete restoration to health. Some retain a bacilluria, but they remain well and show no symptoms whatever. Some people have a pyuria evident to the naked eye for many years without any symptoms. Others retain a permanent bacilluria and are liable to recurrent attacks of pyelitis or cystitis. These chronic bacillurias are very resistent to treatment with antiseptics, alkalies or vaccines. They are probably the result of inefficient or incomplete treatment in the first instance.

Biliary Tract.—If diagnosed early and treated thoroughly, the result should be just as good in infections of the biliary tract as in the urinary tract infections. If treated indifferently and leisurely there is the same liability to relapse and chronicity. Gall-stone trouble may appear later in life. The symptoms often linger unrecognized for years and the continued persistence of the local inflammatory process naturally interferes with successful medication.

TREATMENT

Anything that tends to hold up the passage of urine may help the B. COLI to establish a footing in the urinary tract. Therefore, before commencing treatment it is well to look for any contributory cause of this infection. The presence of bacilli in the urine may not be the only aspect of the trouble from which any patient may be suffering. Other causes may be present, some of which are not generally recognized, or, if recognized, are neglected. Ralph Thompson gives a fairly long list of such causes. But there are a few common conditions which often complicate this infection, phimosis and meatal stricture, urethral stricture, enlarged prostate, nervous diseases, deformities of the bladder due to pressure of uterus, and fistulous

connection between the urinary and the alimentary systems. Many failures in the treatment of B. COLI infections arise from overlooking the presence of such additional factors. Many of these complicating conditions may not be amenable to direct treatment; yet, mere drugging or injections of vaccine without an adequate knowledge of the cause of the chronicity in these cases would be very empirical indeed.

The treatment of B. COLI infections could be described under the usual headings—

General measures.

Drugs — alkalies; antiseptics.

Vaccines.

Diet.

General Measures.—Treatment of acute pyelitis should include rest in bed, warm baths, and liberal intake of fluids. Fruit juice and plenty of weak tea are useful and make the patient feel grateful. Some physicians do not like much milk. Before proceeding further, it is necessary to regulate the bowels. Constipation is commonly present in these cases. Whether or not it has anything to do with the beginnings of the disease, its presence certainly hinders the patient from quickly getting rid of the infection. It is, therefore, essential to attend to it. In the diagnosis of constipation, it would be wrong to depend entirely on the patient's own diagnosis. The physician should satisfy himself that there is stasis of faeces in the lower part of the rectum; the patient should have a palpable pelvic colon and caecum. In some cases the ascending colon can be felt.

Drugs.—**Alkalies**—The rationale of alkaline therapy in acute B. COLI pyelitis and cystitis is little understood. There is an impression in the minds of medical men that B. COLI thrives in acid urine and that alkaline urine is unfavourable to its growth. On this belief is based the usual routine of exhibiting alkalies in the early stages. But, really, B. COLI is indifferent to the reaction of the medium within certain limits. It has been shown by Shohl and Janney that the bacillus can thrive in urine up to *p*H 5.2 on the acid side and that it is inhibited only over *p*H 4.6 to 5.0. At the other end, the growth of the organism is inhibited only when the medium is rendered alkaline to the limit of *p*H 9.2 to 9.6. It is generally impossible to render the urine more alkaline than *p*H 9. Whatever the theory, the practical effects of exhibiting alkalies in B. COLI infections are

well known. The immediate result in a patient is remarkable and constant. The symptoms are greatly alleviated. Often they disappear entirely. And, in acute cases, and in a very large number of chronic ones without complications, it has been found that a systematic and intensive course of alkaline medication completely cures the disease.

The drugs that are generally prescribed with this purpose are many. In many hospital pharmacopœias, there are alkaline mixtures which contain a number of alkaline drugs with some antispasmodics. There is really no virtue in combining a number of alkaline drugs at the same time. Any one of them given alone would be enough. **Potassium citrate** in sufficient doses is as good as any other and more effective than most others. About 20 to 30 grains of the salt fourth-hourly would be a reasonable start. The dose is increased as necessary. Our object is to render the urine rapidly alkaline and maintain it as such, so that each specimen of urine passed turns red litmus paper blue. Some physicians give the drug both day and night so as to obtain an equal spacing of dosage. This is said to maintain the urine at a constant level of alkalinity. While the urine is getting alkalinized, the temperature drops down, and the scalding dysuria and other painful symptoms disappear. The patient feels grateful for the remarkable change from intense agony to almost immediate freedom from pain. This is not an indication for slackening the treatment; on the other hand, it is important to continue the alkali for a week or ten days after the temperature has come down and other symptoms have disappeared.

Antiseptics—Generally, after alleviating the symptoms, it is usual to follow up with a course of antiseptics. There is a variety of these on the market, and probably each physician has his own favourite. But the product which is most commonly used is **hexamine**. It is probably still the best. Hexamine is effective on account of the formaldehyde radicle which is set free when it comes in contact with acid. It is, therefore, essential that the urine should be acid before the drug could be effective. And since the urine has been intensely alkaline previously it should be acidified before hexamine is prescribed. Till recently *acid sodium phosphate* has been the agent used for this purpose. It has the disadvantage that when prescribed in a mixture with hexamine, the formaldehyde is slowly given off in the bottle itself, and that there may be very little of it active when the medicines reach the urine. It is, therefore, necessary to prescribe hexamine and the acid phosphate separately. In the doses usually pres-

cribed this salt does not make the urine acid enough. *Ammonium chloride* is more useful and is, therefore, the one most popular with the profession.

When it is desired to exhibit hexamine where the urine is alkaline, one or other of its combinations, like HELMITOL or CYSTOSPURIN, is used. There is nothing to recommend this procedure in B. COLI infections. And in other cases where the urine is alkaline or ammoniacal, despite all efforts at acidifying with different drugs, other methods than drugging would be needed to control the cystitis, such as lavage of the bladder.

If an antiseptic is required, it has already been said that hexamine is about the best at present available. One would, therefore, like to know if hexamine has no drawbacks as an urinary antiseptic, and whether it is always effective. There are certainly cases of B. COLI infection of the urinary tract where hexamine fails. This is probably because it is not converted into formaldehyde in these patients. There are again some patients whose bladders cannot tolerate any hexamine. Even the minutest trace of formaldehyde in the urine in such patients may cause a very intense irritation of the bladder. This intolerance to hexamine might be sometimes an acquired defect. I have known a patient who was taking hexamine in 10 grain doses three times daily with acid sodium phosphate for months without any ill-effects. After an interval of about a year there was a relapse of his cystitis. He was then put on urotropine. Aften taking 4 tablets, i. e., 2 grammes in 24 hours, he developed a very severe irritation of the bladder. He was then put on ordinary hexamine in the hope that it might be better tolerated. But there was no improvement in the irritability of the bladder.

A patient who was suffering from B. COLI infection of the urinary system and whose urine was acid and loaded with pus cells was put on 3 tablets of urotropine a day. The urine cleared up remarkably within 24 hours. But the clearer the urine, the greater was his distress and dysuria. The patient was not taking as much water and drinks as advised. We occasionally get such patients who do not for some reason take plenty of fluids. Hexamine should be prescribed with great caution in such cases.

While on the subject of hexamine, I should like to refer to the various methods adopted in its administration. There is evidently a belief that severe cases require intravenous medication and that adminstration by mouth is only useful in mild cases. It is difficult to understand the reason for this belief. The seat of the mischief is in the

kidneys and the bladder. Whether given by the mouth or intravenously, the drug is effective only when it is excreted in the urine. Hexamine is a very soluble product and it is rapidly absorbed from the gastric mucous membrane into the blood stream. It has great penetrability. It is distributed through all the tissues and secretions and excreted mainly in the urine. This excretion by the urine starts within eleven minutes after its administration, whether this is done by the mouth, rectum or the subcutaneous route. It finds its way to the cerebrospinal fluid in 30 to 60 minutes of such administration. There cannot, therefore, be any justification for giving hexamine intravenously even in the most severe case of B. COLI infection of the urinary system. Intravenous use of hexamine might be more useful in B. COLI septicaemia. But such cases are rare. For, as already mentioned, when bacilluria begins bacteriaemia ends. Even in cases where there is real septicaemia, hexamine cannot do much good. Hexamine as such has no antiseptic power. In solution it dissociates slowly with the evolution of formaldehyde which is the really antiseptic part. The degree of this decomposition depends entirely on the acidity of the fluid. In neutral or alkaline fluids this evolution of formaldehyde is practically *nil*. Therefore, the power of hexamine to sterilize an alkaline fluid like blood is certainly problematical. Intravenous hexamine therapy is not difficult, nor is it dangerous to the patient. But those who have noted the severe rigor that not rarely follows this procedure would certainly like to spare their patients this severe distress when they realize that hexamine is as effective by the mouth as when given into a vein. Other products like cylotropin are certainly not generally superior to hexamine. There is no special indication for their use.

The alternating treatment.—A method ot treatment which has been very much in vogue with some workers is the one where alkalies and acids are given alternately for some time. This is evidently based on the view that alkalies merely inhibit the growth of B. COLI and markedly ameliorate the symptoms and that hexamine is required to kill the organism. This is theoretically sound, But it has already been shown that alkalies by themselves are capable of curing a very good number of B. COLI infections and almost all cases in obstetric practice. Similarly, hexamine in acid medium is also capable of killing all the colon bacilli.

It is possible that by putting the patient on this alternating course we prevent the bacillus from developing any drug resistance to hexamine,

We have no knowledge on this point. Another and more probable explanation for this procedure should be mentioned. Since hexamine acts best in acid urine, continued acidification of the urine at the necessary high level might induce cystitis. To prevent this is interposed the alkali week. But, as would be presently seen, such complications are exceptional. And since alkalies by themselves or hexamine and acid alone could cure most cases, there could be no justification for this clumsy procedure as a routine measure. It would certainly be useful in exceptional cases where the bladder is irritable to acid.

Exceptional cases.—While the treatment discussed above is generally successful, we occasionally come across cases which behave rather differently and tax the equanimity of the physician and the endurance of the patient.

CASE: The patient, male, age 52 years, health generally fair. While on a voyage he was suddenly siezed with frequency of micturition and burning. His temperature was between 99° and 100° F. He was diagnosed as a case of B. COLI cystitis and treated accordingly. He was completely relieved of all symptoms. After returning to India, he placed himself in the hands of a physician who put him on hexamine and acid sodium phosphate mixture and alkaline mixture on alternating weeks. This went on for months during which he had about a dozen injections of B. COLI vaccine. He was feeling quite well and was not inconvenienced by any urinary symptoms. Suddenly, about two years after the first attack, he had a recurrence of the trouble. His temperature was between 100° and 101° F. He was treated with alkaline mixture. His symptoms were relieved. The temperature came to normal. But the urine was getting more cloudy and pus cells were plentiful. The patient was given *Pyridium.* As a result the urine cleared up remarkably and he was feeling well, gradually returning to his usual diet, though the urine showed a few pus cells yet. But at the end of a week of this state of well-being there was fever and dysuria. Pyridium was given up and the patient was treated with urotropine by mouth and acid sodium phosphate. In a couple of days the fever went down. But micturition was still frequent and the dysuria still persisted, sometimes severe, sometimes mild. While still taking urotropine at the end of a week, the patient had severe rigor and the temperature shot up to 103° F. The temperature came to normal next morning. But in the afternoon there was again a similar rigor and the temperature went up to about 105 . And again on the third day, there was rigor and fever, but

much less than on previous days, the temperature not rising higher than 102.5°. At this stage daily lavage of the bladder was started. His temperature was never high after that. But his urinary symptoms did not disappear. Sometimes his micturition was frequent and painful and at other times he was free while on the same course of treatment. Autovaccine was commenced and a fortnight after that his temperature kept perfectly normal. But even after this urinary symptoms were still unsettled. It was noticed that urotropine when given for over a day (i.e. 1. 5 gm) produced severe pain and burning and irritability of the bladder, the patient desiring to pass urine every hour or half an hour. When the urotropine was stopped and he was put on alkalies, the patient was comfortable, but if the alkalies were continued for a day or two the pain and frequency were just the same as if he was on urotropine. This was the most curious thing noticed in this case. Finally, all the usual remedies were discontinued, and he was put on *Coprakol* (hexyl-resorcin in olive oil) capsules. From this time the patient felt more comfortable, the frequency gradually disappeared, and he returned to normal state in about a fortnight. His urine was generally clear, but there were still a few pus cells in centrifuged specimens.

Vaccines.—B. COLI vaccine is used very much in the treatment of this infection. But its place and importance is not quite clear. I have not had much experience with this line of treatment. I shall, therefore, content myself with giving a resume of the opinions on the subject. (1) Autovaccines are more effective than stock vaccines. (2) Vaccine is more useful in B. COLI infection of the urinary tract than in infections elsewhere. (3) In the early acute stages vaccine is unnecessary and may be harmful. (4) In some chronic cases it is definitely harmful, since it may light up quiescent conditions. (5) Though vaccines may improve the condition of the patient in a general way, they may not succeed in clearing up the local condition completely, for example, pyuria may yet remain. (6) When it is decided to exhibit vaccine, the initial as well as the succeeding doses should be small. There is no advantage in giving large doses. They are generally harmful.

Chronic cases.—B. COLI infections when treated early and in the acute stages are generally easily cured. But chronic cases, i.e., cases that were not correctly or sufficiently treated in their acute stages, and the large group of silent infections that are generally, discovered and treated

long after the commencement of the infection, do not respond to treatment so well. In a large number of such refractory cases, some contributory cause of complication is generally present. These cases should, therefore, be fully investigated, pressing into service all the available modern methods, i.e., direct visualization of the interior of the bladder, ureters and the pelves of the kidneys by a skilled surgeon, and X-ray visualization after the introduction of radio-opaque material. Some of the more common contributory factors which interfere with successful treatment have already been mentioned. A particular physician might have been uniformly successful in curing his cases of B. COLI infection of the genito-urinary tract with a certain line of treatment. But, however infallible in other cases, any treatment is doomed to failure if it does not take into account the existence of such additional factors.

In spite of all care and perseverance, there are still a fair number of patients in whom it has not been possible to eradicate the infection completely. A better knowledge of the cultural reactions of the B. COLI has in recent years enabled some workers to succeed in a portion of such difficult cases. B. COLI grows well in urine with a *p*H of 5 to 9. Growth is inhibited at *p*H 4.6 to 5 on the acid side and 9.2 to 9.6 on the alkaline side. It is impossible to render urine more alkaline than *p*H 9. Attempts have, therefore, been made to increase the acidity. The acid sodium phosphate which is generally used has been found ineffective to increase the H-ion concentration to the required degree. Ammonium nitrate, benzoate or chloride has been found to increase the acidity to a much greater extent. But when the urine is made intensely acid by these means, some patients suffer from irritability of the bladder, and there is fear of chemical cystitis complicating the case. To get over this difficulty Anson L. Clark and H. F. Helmholz of the Mayo Clinic suggested the use of a **Ketogenic Diet.** With such a diet they have been able to raise the acidity of the urine sufficiently high to sterilize it. Helmholz was able to sterilize the urine by raising its acidity to *p*H 5.0 by means of drugs. But with this diet he was able to achieve the same result when the urine acidity was only *p*H 5.5.

This diet was originally introduced as a cure for epilepsy. In essence, the diet is made of a minimum of carbohydrate, a maximum of fat and a moderate quantity of proteins. An ordinary diet contains about 300 grammes of carbohydrate. In the ketogenic diet it is cut down to 30 grammes or even less. The proteins are limited since they yield a fair proportion

of carbohydrate. The effect of such a diet in suitable cases is to produce ketones which are passed in the urine. This increases the acidity of the urine. In most cases, particularly in adults, this diet alone is not enough to raise the acidity to the required degree. It has to be supplemented by drugs orally. Ammonium nitrate, about 6 grammes per day in 12 enteric coated pills of 0.5 g. each, is generally sufficient.

Treatment of B. COLI infections of the urinary tract with the ketogenic diet has yielded some remarkable results. Cases which have resisted other forms of treatment for months and years have yielded rapidly, ending in complete cure. This line of treatment seems to be particularly successful in children. The results are not quite so full in adults, some cases still being refractory. There are great limitations to this treatment. Some patients cannot stand this diet. Some fail to digest fats, and among those who are well able to digest fats, there are some who fail to show any ketone in their urine. Others develop ketonuria without any hyperacidity of the urine. In such cases this form of treatment is unsuitable.

It generally takes three weeks' dieting in cystitis before the urine culture is sterile and another week's regimen is necessary before the patient can return to a mixed diet. A much longer period of dieting is required in cases of pyelitis. If the kidneys are much damaged the patient is unable to excrete enough ketone bodies or sufficiently acid urine to inhibit the growth of the organisms.

While the beneficial effect of a ketogenic diet in certain cases of chronic B. COLI infections of the urinary tract is undoubted, it is yet too early to say whether it could be utilized in the generality of cases. As Cabot, in reviewing the work of Helmholz and Anson, suggests, this treatment might be more successful in those whose ordinary diet differs very materially from this special one. Even otherwise, a diet such as is recommended is certainly very unpalatable, and sometimes produces intense nausea and vomiting. If the vomiting is severe and persists, the treatment should be stopped. Further, the success of the treatment depends on the combined work of the bio-chemist, the bacteriologist and the clinician, a condition that is ordinarily available only in institutions.

STREPTOCOCCAL DISEASE

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The advance in the science of Bacteriology promises to bring about a new orientation in the nomenclature of bacterial diseases on the basis of the causative organisms, the behaviour of which in contact with various tissues in the body is peculiar to each individual member of the pathogenic group. The nature and course of streptococcal disease are distinct for this organism, in whatever tissue or organ it operates. The violence of the inflammatory phenomena, the diffuse phlegmonous or erysipelatous condition, the rapid and extensive suppuration in serous cavities, and the ease with which generalised septicaemia declares itself, are highly characteristic of streptococcal disease, wherever the infection had originally started. The invaders deal a staggering knock-out blow to all the physiological functions of the body quite unprepared for the shock. As the cure of any bacterial disease can be effected only by the attainment of a carefully developed immunity against the organism implicated, whatever the line of treatment, it is reasonable to argue that diseases would be better named in relation to the microbe against which we have to immunise, than in relation to the individual organs of the body. Moreover, when any organ is the seat of bacterial disease, the chances are that the specific disease may overflow and spread to other organs or to the whole body; and the treatment has consequently to be, from the first, directed against the organism rather than aimed at the saving of the organ primarily affected.

I have selected streptococcal disease as a type of bacterial disease, chiefly because the specific treatment (by vaccines and sera) in this disease has given me encouraging results—results that stand out as a sign-post signifying the direction for our advance along the road to the real cure of disease by immunisation. Further, in its highly virulent role the ubiquitous STREPTOCOCCUS is an organism a very few individuals of which are capable of producing the most alarming symptoms of generalised infection within a short period of incubation (in from 16 to 48 hours) in apparently healthy individuals. The time has gone by when every case of systemic streptococcal sepsis was regarded as a primary inoculation from

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without; and it is now realised that latent and chronic foci of streptococcal infection can precipitate a general septicaemia under conditions of lowered resistence of the body and exalted virulence of the organisms. In practice one meets with cases, where, with all the care of asepsis and studied non-intervention, puerperal septicaemia followed confinement of women in whom the misfortune was feared from sepsis of the mouth or of the skin inadequately treated during pregnancy. I can recall to my mind certain cases of impetiginous lesions of the leg (for which a haemolytic STREPTOCOCCUS was responsible) where the auto-vaccine was half-heartedly given during pregnancy; as was feared, the women developed puerperal sepsis: and swabs from the uterus gave me pure cultures of the STREPTOCOCCUS answering all the biochemical tests as the cocci from the primary skin lesions. The treatment by the first vaccine from the original skin lesions brought about a recovery from the uterine complication. Of course, not all cases of chronic skin or dental disease of pregnant women result in puerperal sepsis. But the fact that puerperal septicaemia is still with us in spite of all our asepsis and antisepsis cannot redound to our credit. If it is humanly impossible to discover all cryptic foci stowed away in remote parts of the body, there need be no insuperable difficulty in recognising the fully developed septicaemic condition that is too often labelled 'malaria.'

The portal of entry of the organism is a breach in the skin or mucous surfaces. If they are not ejected forthwith from these locations, they may be arrested in their advance, either near the entrance, or in the subjacent lymphatics (with consequent impetigo, erysipelas, lymphangitis, or lymphadenitis); or in the subcutaneous tissues causing cellulitis or circumscribed abscesses. If the defence is inadequate or ill-sustained, the invaders sally forth into the blood circulation from where they retreat to their base, or push forward and capture deep and vital organs. Blood cultures will be positive only if the blood is drawn during one of the sallies, that is, when there is an accession of fever with rigors; and one single blood culture should not mislead us into the error of excluding bacteriaemia. A few cocci fished out of the blood do not necessarily signify an actually infected or septic condition of the blood, as the enemy may occasionally be caught within our lines, in battle, although our main defences are intact. STREPTOCOCCI can be eliminated or extruded through the urine or the bowel from the body, without the kidney or bowel being infected; occult streptococcal infection has often been so revealed in the urine or the motions

in certain obscure diseases improving under vaccine treatment. If only a few stragglers enter the blood, alive or killed by the leucocytes, their presence would help to provoke and stiffen the defences in the tissues by rousing the defensive mechanism, just as a dose of vaccine given by the intravenous route would do. Indeed, it is reasonable to suppose that we acquire our natural immunity to diseases by our being unconsciously inoculated by bacteria prevalent in our environment; and it is equally rational to expect an infection to be overcome by carefully imitating the graduated inoculations of Nature. Persistent flooding of the circulation by large bodies of cocci and their multiplication in the blood itself results in septicaemia, the dangers of which are the scattering of the organisms and their lodgment in damaged or over-worked organs with delicate and intricate capillary structure, causing pneumonia, endocarditis, nephritis, synovitis, and other complications. Too often the physician is confronted with the secondary complications where the primary affection was over-looked or not treated properly by the uninitiated.

The lesions that STREPTOCOCCI exhibit in the body are numerous. They may be acute or sub-acute; and superficial or deep. Among the superficial lesions may be mentioned erysipelas and impetigo (subacute and acute bullous.) A rapid spread (that is, with a short incubation period of 16 to 48 hours, as has been mentioned), with vesicle or pustule formation, and a marked red areola and subsequent discoloured dark scar, are characteristic of streptococcal disease. The slighter skin abrasions open the passage for the cocci into the superficial lymph radicles where there are few opposing phagocytes; fighting shy of the phagocytic blood stream, the organisms in this case establish a superficial erysipelatous condition in which immune therapy of the blood is of little effect, except to prevent deeper invasion—by general immunisation. But deeper abrasions where the blood cells enter into the fray, tend to develop localised skin lesions or cellulitis according to the resistence encountered. On mucous membranes, the important lesions are '*Ludwig's Angina*' or erysipelas of the mouth and throat, and the condition of sepis of the uterus in abortions (especially criminal abortions) and in the puerperium. STREPTOCOCCI should be strongly suspected when there are observed, as in the throat, sudden pain and marked swelling and oedema, with induration and perhaps dyspnoea, aphonia, dysphagia, and fever with rigor, delirium and other symptoms. The deeper lesions, among which cellulitis and septicaemia are the next in the order of advance, also indicate the streptococcal nature of the disease

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by the sever rigor and the wide range of remittent temperature, the rapid and compressible pulse, the marked prostration, the sallow skin (seen especially with cocci that haemolyse the red blood cells)—the pallor of which marks the intensity of infection, and later, pus formation and pyaemia pointing to the penetration of the cocci into the deeper organs. When primary surface lesions are not obvious, a blood film should be examined for malaria, and any departure from the normal polymorph leucocytes noted for comparison with future findings. If a discharge is obtainable, a gram-stained film would at once reveal abundant STREPTOCOCCI, free and phagocytised. A fever continuing for over two days, that shows no malarial parasite in the blood, should call for the blood culture, to be repeated if negative at the height of the fever. A number of media, both liquid and solid, should be inoculated with the blood; the solid media would probably yield the quicker result in 24 hours. The pathogenicity or virulence of the cocci may be taken for granted if the inoculated fluid media produced conspicuously long chains of stout cocci that take on an unusually deep staining. The diagnosis of acute streptococcal infection is established when the laboratory reports the presence of the cocci in numerous colonies on the solid media with the above characters. In any case, it is important that malaria and typhoid fever are excluded by the blood film and culture tests, aided by leucocyte counts, so that we may avoid unnecessary quinine drugging, and have a freer hand to feed the patient with nourishment sufficient to overcome the infections. Having diagnosed the specific nature of the disease from the foregoing, we shall now proceed to the treatment of streptococcal disease.

Knowing the propensities and disposition of the invading hosts our campaign should be suitably planned. We have to reckon with the rapidly multiplying cocci, the accumulating toxins that depress cell vitality and jeopardise the normal functioning of vital organs, and the possible accumulations of dead tissue and debris that form a reservoir for the live organisms. The indications for treatment can be outlined briefly before we take up the means of attaining them. As regards prevention, the obvious thing is to isolate infected cases. Certain morbid conditions of the blood (as in diabetes) that predispose to coccal invasion should be corrected (by insulin if necessary) and oral hygiene practised side by side with the inclusion of appropriate foods (containing vitamins and calcium) that prevent dental deterioration preparatory to dental sepsis.

In the treatment of the developed cases, the principal indications directing our attention are (1) the eradication of the infected foci where the enemy are garrisoned as it were in readiness for opportunities for assault; (2) the mobilising of our defensive reserves from all sources available in the body, so that the cocci will be opposed by forces securing immunity from invasion; (3) by invoking the aid of extraneous agencies or 'mercenaries' from without; (4) by ordering the normal bodily functions to be carrred on, with as little dislocation as possible of the digestive, excretory, circulatory and other systems, pending the rescue and recovery of tissues damaged by the concomitant toxaemia of the invasion. How shall we translate these therapeutic indications into actual practice?

(1) The eradiction of septic foci is a pious formula easier to preach than to carry out. Whether we look upon these foci as remnants of enemy detachments or bandits not completely swept away by an immunity just sufficient to overcome a previous general infection, or as independent centres of primary mischief, it is a safe practice to assume that most adults, except the very robust, would be harbouring the common cocci somewhere in the system. As any operation on a subject is temporary depressant of his innate resistance, it would be an advantage to raise this resistance or immunity against pyo-cocci before undertaking an operation. A history of past sepsis or a general run-down condition would strengthen the case for enhancing this immunity. A few doses of stock pyogenic vaccine, given for about two weeks before an operation, would, I believe, materially reduce the risk of sepsis.

In dealing with skin lesions in the presuppurative stage, ointments of ichthyol are usually applied. A paste of magnesium sulphatewith glycerine, covered over with an impervious tissue, by its dessicating and sedative action, often absorbs these conditions, with the general treatment and a few doses of a stock polyvalent 'sensitized' vaccine. If the morbid process extends along deeper planes, with possibly pus-formation and cellulitis, free incisions must be made, along which the pus and and toxins may make their exist when the drive from behind gains strength under reinforced resistance. Hot dressings of a saturated sterile solution of magnesium sulphate are helpful in extracting toxins from the tissues by their osmotic pull. The curetting of an infected wound (in puerperal endometritis) is no longer in vogue, as this proceeding might force the cocci into the deeper tissues. Even here, the need for free drainage is paramount.

When we have carried out the measures directed to the primary focus, we turn our attention to the next indication: (2) that of mobilising the defensive resources of the body. To achieve this, the treatment by the streptococcal vaccine is, in my experience, pre-eminently the method of choice. A disease gets a foot-hold in the system during the ebb-tide of its opsonic power and recovery demonstrates that the body can be trained or educated to regain its lost powers. The natural recovery of immunity is not likely to clear up residual foci in every case; and, therefore, it would facilitate complete recovery if the degree of immunity is exalted and sustained at a high pitch by artificial means. For some unexplained reason, the immunity response to streptococcal vaccine declares itself remarkably early (within a day or two) in acute cases, in contrast with the period that we know to be necessary to bring about immunity in preventive inoculation as in typhoid where the tissues are resting and not 'sensitized' by a provocative organism or 'antigen'. The suitability of the case for vaccine therapy should be carefully considered. As a rule, vaccine treatment is absolutely contra-indicated if an active focus of deep sepsis is suspected. When deep lesions (especially visceral lesions) are excluded, vaccine should be given for superficial lesions or lesions that can drain out freely. Closed suppurations are dangerous conditions for vaccine therapy, and should be religiously avoided. A single effective dose of vaccine would soon stir up a well-marked defensive reaction with increased discharge from wounds—the enemy executing a hurried retreat with the deadly toxins that would have poisoned the body. In a case of extensive cellulitis of the arm, in a Brahmin of 63 years, inadequately treated with pastes and oils, a single dose of stock vaccine, administered after multiple incisions and evacuations of much thick pus, completely changed the outlook. In less than 24 hours the ample dressing was soaked with profuse sero-sanguineous pus of a thinner consistence. Imagine a case of streptococcal appendicitis for which a dose of vaccine is given without an operation and drainage. An unruptured appendix would in a few hours be distended with pus under high tension by the reactive effusion under the stimulus of the immunisation. The risk is the imminent rupture of the appendix filled with a more diffusible pus before any walling-off adhesions could be formed. In acute periostitis or osteomyelitis, the drainage of all pus before vaccines is the rule. Multiple foci of suppuration confront us with the more difficult problem of eliminating deep foci. Nevertheless all the obvious seats of suppuration should be dealt with; and

if the septic fever continues unabated, no vaccine is advisable in these. Next in importance to 'drainage before vaccines' comes the sizing of the doses in given cases. For cases of ordinary pyococcal inflammation, before suppuration, very small doses of vaccine may be tried. A boil may thus be absorbed by a 50 million dose of staphylococci, gradually raised to 100 millions and 200 millions daily or on alternate days, watching for the softening of the boil. Streptococcal abscesses are more often isolated or single (though not always so), unlike staphylococcal abscesses that usually are multiple. My practice has been to start with a dose of 10 millions of streptococci in the average cases, as a cautious ('feeler') dose or a reconnoitring dose. If no marked reaction occurs and no deep lesion is revealed in 24 hours, 20 millions or even 50 millions are given on the second day. Some practitioners start with doses of 100 millions or 200 millions for rapid effect. Perhaps a small first dose errs on the side of safety. However, cases differ as regards dosage, a debilitated patient being unable to withstand a reaction that a robust individual can. The dramatic clearing up of extensive suppurations is seen in no bacterial disease as in streptococcal infections. I have used as a routine 'sensitized' vaccines, the live cocci being treated with the serum of immunised rabbits or commercial sera. Intolerance sometimes develops, more especially with staphylococcal vaccines, after a certain strength of the vaccine has been reached.

A reduction of the doses and a wide spacing of them, or a repetition of the optimum dose about every week or two, are indicated in such. In treating an acute infection, it is of the utmost importance to avoid superimposing 'negative phases' by overdoses of vaccines; indiscriminate massive doses would retard recovery from the disease. But, in chronic affections, much larger doses may safely be given, as the discrete foci with their ring of connective tissue prevent the free access of the organisms into the circulation and the reactions are less severe. The immunising mechanism should not be thrown out of gear by an abrupt rise of the dose. I can recall a case where a doctor by mistake injected the 6th dose where the 1st was advised; the patient survived the mistake, but would have no more of the vaccine treatment! All vaccines are poorly tolerated in advanced diseases of vital organs. In chronic endometritis of streptococcal origin, with repeated abortions and with no sign of the syphilitic taint, vaccines prepared from the menstrual discharge have given me encouraging results, healthy babies being born in some of them. The 'stich abscesses' following operations have often cleared up under vaccines prepared from the discharges. I would

not recommend the use of vaccines soon after septic operations on the viscera because we cannot be certain that we have drained out all pockets of pus. After all fever has subsided, if the general clinical condition is fairly satisfactory, vaccine treatment may be attempted with comparative safety, as the parts behind would be walled-off by adhesions. The aim here is, as stated already, to keep up the general immunity at a high level, to prevent dispersed organisms establishing subsidary or metastatic foci. In acute endometritis of the puerperium, the onset of rigors following the vaccine has frightened many a medical practitioner. A rigor and a raised temperature are a measure of the desirable resistance of the body; it may also be an indication of an advance of the disease. In both cases it is due to the discharge of a dose of toxic proteid molecules from dead cocci into the circulation. Protein therapy is of benefit in septicæmia, and rigors are courted and induced by physicians in other circumstances. Why then dread a rigor that introduces a very little protein through the killed vaccine besides giving us the chance of development of specific immune bodies later? The intensity of the rigor can be reduced by supplying the body with the anti-toxin (serum) prior to the administration of the vaccine, so that any toxin liberated at the instance of the vaccine may be neutralised. So protected by the serum, the doses of the vaccine, especially of the 'sensitized' vaccine, can be boldly advanced so as to secure a powerful immune response in a short time. Our objective is the destruction or 'lysis' of the organism or 'antigen,' in bacteriological parlance. An 'antigen' undergoes 'lysis' when it meets with an 'antibody' together with the 'complement.' Given the 'antigen' (the cocci), the 'complement' has to be drawn from the natural 'complement' in the patient's blood; a deficiency in the 'complement' can be made good when this principle is imported from a foreign body in the form of the serum from the horse. To effect a 'lysis,' there remains now the 'antibody' to be supplied. This body is sought to be induced from an active stimulation of the body cells, especially the cells of the blood and the reticulo-endothelial system, that may yet have a reserve power of forming them in the presence of the antigen in the vaccine. The invading organism is an insecure source of antigen, because, given a free hand, the living organism in its virulent career produces quantities of toxins that paralyse the action of the cells and perhaps of the natural body 'complement' as well. The toxins prepare the way for the invaders, somewhat in the manner of a 'gas-attack' in battle throwing the defenders out of the

fight. In the vaccine the antigen is supplied bereft of its pathogenic properties and freed from most of the toxins. The three elements, the antigen, complement and antibody being now united, 'lysis' results and the infection is overcome. It may seem incredible that a minute dose of dead cocci can cure a widespread invasion; but it is a proved fact that all bacteriologists would testify with regard to this organism. It may be explained that the vaccine sets in motion, or initiates, a train of catalytic actions that spread (like 'wild fire') to the entire body cells, suddenly restoring the morale of the defenders, as it were, temporarily stunned by the onset of the invasion. The clinical signs of reactivity to vaccines are a more practical guide to treatment than opsonic estimations; hence the importance of the clinician and the immuniser acting in collaboration if immune therapy is to advance.

(3). The third indication for treatment is the substitution of 'mercenaries' when the defenders are paralysed or disarmed. Under the circumstances, they are unable to elaborate effective antibodies or antitoxins; and they may also be faced with a deficiency of 'complement.' Prepared antisera contain the antibodies. These may be given in doses varying from 20 to 100 c.c. daily for seven days with the usual precautions. One should never think of intravenous serum injections in patients in whom the integrity of the vascular system is in doubt; a violent protein shock may here result in a vascular rupture. Blood transfusion is now resorted to with success. Besides supplying reinforcements of the cellular constituents, the fresh serum brings in the precious 'complement', in addition, to the exhausted patient. Intravenous injections of drugs have not realised the promises once held out. Mercurochrome and trypaflavine were given a trial in several cases with little encouraging results.

(4). The fourth indication in the treatment is the ordering of the smooth working of the normal functions of the body generally. The internal government cannot be neglected when a state is at war with an external enemy. The defending cellular units have to be fed with a sufficiency of nutritious materials in an assimilable form. The basal requirement of about 12 calories for every pound of body weight should be provided. To a man weighing a hundred pounds, 1,200 calories derived from starch gruels, broths, eggs, milk and other foods in a digestible or pre-digested form should be prescribed. (Roughly, the caloric value of an ounce of milk = 20; of egg (i.e., one egg) = 80; of sugar = 113; of starch = 100; of broth = 5, of orange juice = 12). A liberal diet is to be given in this disease,

unlike in typhoid fever. The importance of excluding typhoid by careful diagnosis is clear. When the digestion and assimilation are very poor, repeated glucose solution is to be given by mouth or intravenously, insulin being used if necessary even in non-diabetics. Liver extracts (e.g., 'campolon') are suggested to stimulate the hæmopoietic system, as an alternative to blood transfusion. Diluent drinks are to be freely supplied to dilute the toxins and liberate the cells. Massive doses of quinine and iron are not advisable as they can easily upset the digestion and render the prognosis grave. The excretory organs have to be watched with extra care. The bowels should be kept on the free side (without exciting diarrhoea) by magnesium sulphate, 60 gr. to 120 gr., every morning. Body baths by sponging are to be daily given. To facilitate the elimination of the cocci and the toxins along the kidney without damage to the organ, fluids and even alkalies should be administered, as mentioned above. Congestive signs of the lung bases may call for stimulating liniments or poultices. The heart usually calls for support at times. It is safer to digitalise the myocardium if the organ is likely to have to face a severe crisis, adopting the rapid method of digitalisation by the tincture. Lack of sleep should be particularly treated, if necessary, by hypnotics such as Adalin, Chloralamide, or Medinal, it being important that the labouring organs secure the rest that recuperates vitality.

To recapitulate: a microbic disease can be cured only when the body regains its suspended immunity to the organism concerned. And while the usual methods of treatment prepare the system for a favourable termination of the infection, the parenteral administration of the specific 'antigen' or vaccine seems to be the quickest and the most direct means of stimulating or conscribing the remote cells for the service of the body, as exemplified by their behaviour under the stress of active streptococcal immunisation. Animal life is rendered possible by the acquisition of herd immunity provoked at the instance of the bacterial antigens of our environment, in contact with the natural resisting powers of the tissues. The witch-doctor, the medicine-man, the barber-surgeon, and even many of the later physicians of our age are merely helping, indirectly, by general therapeutic measures, the restoration of the intrinsic resistance of the body to microbic invasion. Systems of treatment that do not recognize the existence, or the specific nature, of the causative organisms of disease, cannot naturally be expected to avail themselves of the advantages of immune therapy. The infant science of Immunology, for all its short-comings and its uncertainties, suggests to us the basis on which all rational therapeutics have to be considered. The goal of the clinician and of the immunologist are identical. It is devoutly to be hoped that physicians and surgeons of to-day would interest themselves more actively in this infant, and not segregate this off-spring of our science in the confined and stifling atmosphere of a stereotyped public health laboratory.

RADIUM THERAPY

IN BENIGN UTERINE AFFECTIONS AND CERVICAL CARCINOMA

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RADIUM: HISTORICAL SURVEY, PHYSICS, AND GENERAL PRINCIPLES AND METHODS OF APPLICATION.

Soon after Röntgen's discovery, Becquerel found that Uranium emitted highly penetrating rays. The announcement of the discovery of this phenomenon, later called radio-activity, was made in 1896. The effects of the new radiation were found to be similar to those of the X-rays: that is, blackening of the photographic plate, ionisation of gases, generation of heat, and production of fluorescence.

Further research undertaken by Prof. and Mme. Curie resulted in the discovery of two new radio-active elements, Polonium and Radium.

Radium is, in its elementary form, a metal resembling lead in appearance. As it is chemically unstable in this state, it is employed therapeutically in the form of radium salts, either radium bromide, sulphate, or chloride. Radio-activity depends solely upon the amount of radium element present, and the content of any applicator is, therefore, expressed in terms of the weight of the element. Rutherford has shown that radio-activity is due to spontaneous disintegration or transmutation of the atoms of the radio-active element. This transformation takes place continuously and at a definite rate for each element.

The subjoined Table shows the Uranium-Radium series of elements. Starting with Radium, it will be noted that this element disintegrates to Radon or radium emanation, a gas with an atomic weight of 222. The transformation is associated with the emission of an *alpha* particle which reduces the weight by four. Radon undergoes a similar change, also losing an *alpha* particle with accompanying loss of atomic weight by four. The result is Radium A, which likewise disintegrates, losing an *alpha* particle. The atom is now called Radium B which changes into Radium C. This transformation is different from the preceding ones. There is no reduction in the atomic weight as there has been no loss of *alpha* particle. There is,

however, emission of negative *beta* particles and resultant *gamma* radiation. The *alpha*, *beta*, and *gamma* rays differ greatly in their physical

URANIUM—RADIUM SERIES

Element	Atomic weight	Half-value Period	Radiation symbol	Sequence Emission
Uranium I ...	238	4,560,000,000 years	U I	Alpha
Uranium X^1 ...	234	24·52 days	U X^1	Beta & Gamma
Uranium X^2 ...	234	114 minutes	U X^2	Beta & Gamma
Uranium II ...	234	120,000,000 years	U II	Alpha
Ionium ...	230	74,300 years	Io.	Alpha
Radium ...	226	1690 years	Ra.	Alpha
Radon ...	222	3.825 days	Rn.	Alpha
Radium A ...	218	3 minutes	Ra. A.	Alpha
Radium B ...	214	26·8 minutes	Ra. B.	Beta & Gamma
Radium C ...	214	19·7 minutes	Ra. C.	Alpha, Beta &
Radium C^1 ...	214	1/1,000,000 sec.	Ra. $C.^1$	Alpha [Gamma
Radium D ...	210	16 yrs.	Ra. D.	Beta (soft)
Radium E ...	210	4·98 days	Ra. E.	Beta (soft)
Radium F (Polonium)	210	139·5 days	Ra. F.	Alpha
Radium G (Lead) ...	206	... ...	...	... ...

characteristics. The *alpha* particles are helium atoms minus two electrons. They are active ionizers, but their value in therapy is negligible, due to their lack of penetrability. They are absorbed in 3 to 7 cm. of air or by a sheet of ordinary writing paper. The *beta* rays are negative electrons of varying speed approaching the velocity of light. Their penetrability is approximately 100 times that of the *alpha* particles; swifter ones traverse 1 cm. of tissue and all are stopped by 2 mm. of brass or 0·5 mm. of gold. It has been shown that the *gamma* rays are electro-magnetic waves similar to the rontgen radiation, except that they are of even shorter wave length and, therefore, of still greater penetrability—about 100 times that of *beta* rays. The hardest *gamma* rays can pass through 25 cm. of lead. In the Table is shown also the half-value period, which is the time required to transform half of the atoms of a given element to its subsequent products. For Radium this period is 1700 years, which means that it decays only 1 per cent. in 25 years. Radon, on the other hand, has a half-value period of only 3·8 days, and in 30 days about 96 per cent. of it would disintegrate.

It will be noted that the *beta* and the *gamma* rays are not given off until the disintergration has reached the stage Radium C. Since these rays are the ones particularly used in therapeutics, it is Radium B and C and not Radium itself which is the source of therapeutic radiation. For this reason, the biological action of the Radium element and Radon is alike, except for the diminishing intensity of the emanation. By means of proper apparatus, Radon can be removed from its parent element and used in place of radium salt. In either case, it is the decay products which emit the useful radiation.

There are both soluble and insoluble salts of Radium, and to collect Radon, a soluble salt is put into solution. Radon is given off and is collected and pumped off into a long, slender gold tube. The gold tube is then measured off, and cut into sections (or gold radon seeds--as they are called). Glass seeds were used in the earlier days; but, as it became apparent that glass permitted the caustic *beta* particles to act on the tissues in such a way that an area of necrosis surrounding each seed resulted, this was replaced by gold tubing, which filtered off most of the *beta* rays and prevented this reaction. The gold tubing is cut and sealed by specially constructed pliers, and the exact amount of Radon in each is measured by means of a gold leaf electroscope, so that the dosage can be carefully calculated. The advantage of using Radon lies in its greater flexibility, higher concentration, and reduced financial risk.

The strength of both Radium and Radon applicators is measured by ionometric *gamma* ray comparisons with a standard of known Radium content. The dose, or quantity of radiation given with the element, is expressed in milligram hours, which is the product of the strength of the applicator and the time of application.

The unit of Radon is the milli-Curie, which is the quantity of *aged* emanation that emits the same intensity of hard gamma rays as one milligram of Radium element. Due to the decay of Radon, the dosage in terms of millie-Curie hours cannot be obtained by multiplying the number of milli-Curies with the time of irradiation.

The total dose delivered by one milli-Curie of Radon, during its entire active life of about 30 days, is 133 milli-Curie hours. The dose for any shorter period may be obtained from available tables based upon the decay curve of Radon.

Three general methods of application are used in radium therapy of gynaecological conditions. Radium needles or Radon capillaries are applied

intrinsically by implantation in the tumour itself. Their usual filtration is 0·5 or 0·6 mm. of platinum or equivalent, and may be 1 to 6 cm. in length. Radium needles usually contain 0·5 to 1 mgm. of Radium element per each centimeter of length—termed 'linear intensity'. The definite thickness of the filter is essential to absorb all the caustic *beta* rays, and the definite 'linear intensity' to prevent increased damage to tissues by too great a concentration of radiation. Needles are distributed in the growth 1 cm. apart and left in situ for a period of 5 to 7 days—in implantations one considers the 'necrosis dose', which is reached in 100 to 120 hours when 1 mgm. Radium needle with 1 cm. active length is used.

A more even intensity distribution can be obtained by using various tubular applicators into cavities. Heavier filtration, equivalent to 1 to 2 mm. of platinum (1 mm. platinum=1·4 mm. gold=4 mm. brass.), to cut away even the softer *gamma* radiation is used—this is considered to permit passage of the shorter wave-length *gamma* rays, which have a selective action on the cancer cells, and are comparatively less injurious to normal tissues. These applicators are of varying lengths (1 to 5 cm.) and contain varring quantities of Radium (5, 10, 20, 40 or 50 mgm. Ra. element). These radium containers are covered with rubber to absorb secondary radiation from the filters. The intensity of radiation decreases, according to the inverse square law, with the increase in the distance from the source of radiation, i. e., if a given dose is obtained in a specified time at a distance of 1 cm. from the source of radiation, shifting the source to a distance of 2 or 4 cm. makes the intensity 4 or 16 times less, or it would take 4 or 16 times longer time to obtain the same dosage, respectively.

There are various methods of expressing Radium dosage, but I believe it is best to state clearly the type and distribution of Radium containers, the quantity of Radium in them, the filter, the distance and the time, in terms of S. E. D. (skin erythema dose). A 20 mgm. radium-applicator, with 1 mm. platinum filter, in contact with the skin for 10 hours, causes an erythema in 4 weeks, i. e., 1 S. E. D=200 mgm. hours.

At 1 cm. distance it is about 600 mg. element hours for an S. E. D. and at 4 cm. about 8000 mg. element hours. With increase in the filter and distance, the time factor also increases to deliver the same S. E. D. The E. D. (erythema dose) for mucous membrane is about 75% of that for the skin, and in irradiation of the uterine cervix, the bladder and rectal walls should be so packed away by plugging the vagina with gauze that they are not damaged by heavy radiation.

The advantages of heavily filtered Radium on lightly filtered are–

1. Mucous membranes of the vagina and uterus are not as susceptible to very short wave lengths as they are to longer ones; consequently, a larger proportional dose can be administered with a heavily filtered Radium.

2. Increased time of radiation permits the exposure of a greater number of cancer cells during the time of mitosis when the cells are especially radio-sensitive.

3. Increased length of time permitted by the heavy filtration correspondingly increases the radius of effective radiation.

4. Heavy filtration shuts out all but the shortest wave lengths. These are considered most efficacious in producing molecular death of cancer cell.

5. As a direct result of the factors already mentioned, the percentage of recurrences is greatly decreased over the lightly filtered technique. Wherever a change has been made from a lightly filtered to a heavily filtered radium, improved results have been obtained. These effects have been noted by Kaplan, Regaud, Crossen, Pfahler, Heyman, and others. The rationale of heavily filtered radium has been admirably set forth by Crossen.

Radium can also be used externally in the form of packs, to parallel the conditions of high voltage rontgen irradiation. *Tele-Curie therapy* (radium bomb) is the term applied when such large quantities as 2 to 5 grams of Radium element in suitable heavy lead containers are used for distance radiation. This is practicable only where large quantities of Radium are available.

EFFECTS OF RADIATION ON THE PELVIS

It is Pullinger's opinion (*Lancet*, April 1933), derived from examination of actual organs treated by modern methods, that while selective destruction of tumors only is apparent, the normal cells also do suffer. In order of sensitivity he would place haemopoietic cells a long way in advance of malignant ones; for, to destroy the latter the treatment has to be local, and as high and even an intensity of irradiation as possible must be achieved in the area in which the neoplastic cells are growing; whereas haemopoietic cells are destroyed at even considerable distance from the source of irradiation, where the dose is weak and diffuse. In order to replace the assumptions by observed facts he examined about 100 specimens each of malignant and normal tissue from operations and autopsies, all of which had been treated by Radium or X-rays. The most constant morphological change

found was a lesion of the blood vessels. It started with a simple hyperaemia, but eventually the vessel showed signs of damage, and all the subsequent changes in the tissues could be related to the vascular disturbance. The vascular lesions lead to exudation of serum, to rupture and extravasation of blood, and to thrombosis. The two objections for not accepting these processes as an explanation of tumor destruction have been, first, that the vascular damage was observed in tissue which was the site of previous pathological change—ascribed to tumour degeneration, inflammation around the tumor, and invasion of the blood vessels by the growth—and, second, the unaccounted-for selective action. Pullinger irradiated the abdominal wall of a normal rabbit by means of a wax plaque containing radium needles. No injury was caused to the skin; there was no irritation or erythema. But deep to the uninjured skin, thrombosis was found in numerous vessels in the serous coat of the bladder and accompanying the spermatic cord. Strangeways and Fell demonstrated that thrombosis of normal vessels could occur in the absence of damage previous to irradiation. Damage to the tumour may be more extensive because the dose is concentrated upon it; the vascular supply of the neoplasm is carried on by means of capillaries which are imperfect and extremely liable to damage, and there is no collateral circulation to compensate for the damage.

Radium has a three-fold action on malignant tissue: it affects the cancer cells, the connective tissue, and the blood and lymph vessels. In the cancer cell there is a swelling and vacuolisation of the protoplasm and shrinking of the nucleus. This is followed by phagocytosis and absorption, and replacement by homogenous connective tissue, which contracts and affects the lymphatics and smaller blood vessels, and starves the growth.

INDICATIONS.

Many physicians and laymen think that Radium and roentgen rays are employed only in the treatment of cancer, whereas these agents are not only useful but almost specific in the treatment of certain benign conditions. Moreover, in trained hands, they can be safely and harmlessly used regardless of the age of the patient. In other words, if one knows the biological effects of different doses on the tissues in the field of radiation, and is capable of accurately determining the dosage, the use of Radium and roentgen rays is no less radical than the use of surgical procedures. I am not advocating dispensing with Surgery, for there are many cases for which

Surgery and Surgery only could be used. But in this article I am attempting to deal only with cases of uterine haemorrhage in which radium therapy is the method of choice.

The causes of uterine haemorrhage are malignant tumors, ovarian dysfunction, uterine fibrosis, fibro-myomata, chronic endometritis and metritis, chronic endo-cervicitis and cerivicitis, polypi, pregnancy, endocrine disorders, (occurring at puberty or the menopause), and constitutional diseases. Except in pregnancy, endocrine disorders (in some instances), very large or pedunculated fibroids, pelvic inflammation and certain constitutional diseases, Radium and X-rays, singly or in combination, are indicated in the treatment of the above uterine conditions. Its advantages over surgery are: there is no operative mortality, no infection or shock, a general anaesthetic is rarely needed, and the patient is not confined to bed for a long period of time.

In carcinoma of the cervix, radium therapy, in combination with deep roentgen rays, is the most efficient treatment in use at the present time. On the other hand, except in grade-4 malignancy, fundus carcinoma is best treated by hysterectomy and then radiation. This is especially true if partial hysterectomy is done, for the percentage of cures is greatly increased by heavy radiation of the cervical stump. The very malignant diffuse (grade-4) fundus carcinoma should always be given heavy radiation regardless of whether hysterectomy has or has not been performed.

Regression of fibroids with cessation of the associated uterine haemorrhage following irradiation is well known at the present time. Radiation should be restricted in some cases, in women below forty years of age, where the tumor is quite large and the amount of radiation necessary to effect a cure would lead to an artificial menopause. It is surprising, though, how much can be accomplished with sub-sterilizing doses. Very large or pedunculated fibroids should not be treated by irradiation. Haemorrhage due to uterine fibrosis responds most favourably to either X-ray or radium treatment.

In no other condition is irradiation of more benefit than in cases of uterine haemorrhage due to the menopause. Acute and subacute pelvic inflammation is a contra-indication to the use of Radium and X-rays. On the other hand, old cases of chronic endometritis and endo-cervicitis can be relieved by intra-uterine and intra-cervical applications of Radium. In these cases I have found Radium to be of more value than X-rays.

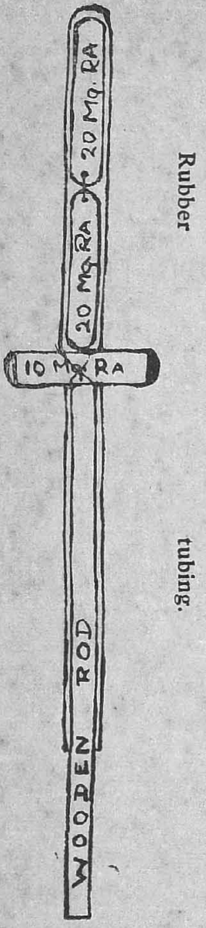
Occasionally, in young girls, at or near puberty, we find uterine bleeding that fails to respond to treatment of any form other than irradiation. Usually such cases can be benefited by very light doses of either Radium or X-rays, and under such circumstances these agents should be used without hesitation.

As to the choice between Radium and X-rays, there is none in many cases. If the disease is confined principally to the cervix, or is located nearer the uterine cavity, Radium will usually be found the more effective. In the larger fibroids or in uterine fibrosis I prefer high-voltage X-rays. In carcinoma of the cervix or fundus I always use both X-rays and Radium.

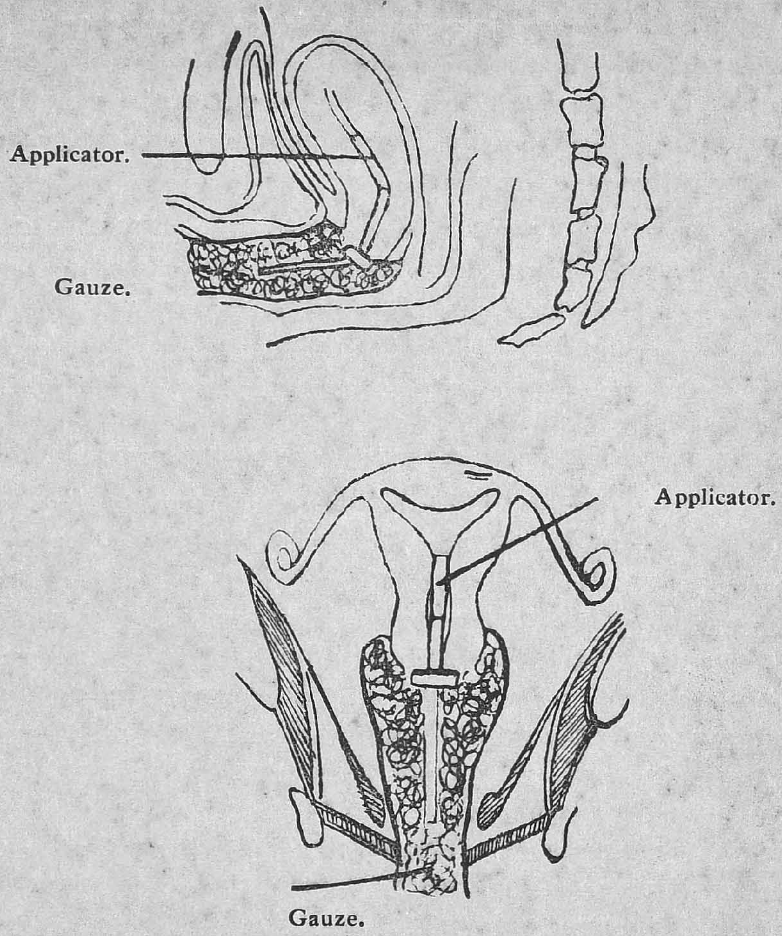
APPLICATION AND DOSAGE.

In most cases of non-malignant uterine bleeding we use a cross-shaped 40 mgm. radium applicator. It consists of two gold tubes, each containing 20 mgm. of Radium, an active length of 2 cm., and a filter equivalent to 1·4 mm. gold, placed in tandem for insertion into the cervical canal and uterine cavity. This is enclosed in a rubber tubing, and a cross armpiece of rubber is placed on the applicator in such a way that it fits snugly against the cervix, when the portion containing the Radium is inserted into the uterus. A wooden rod of suitable dimension is the proximal part of the cross, occupies the vaginal cavity, and helps to hold the applicator in position while plugging the vagina. The whole applicator with the rubber cover will be about the size of an ordinary lead pencil, but much thinner, and being semi-rigid greatly facilitates insertion and placement in proper position. In malignant conditions, another 10 mgm. is put into the cross armpiece, which when in position against the cervix gives an additional source of external radiation and some cross-firing effect.

The patient is given castor-oil and a douche the night previous to the planned treatment, and several cleansing enemas and a douche the following morning. A general anaesthetic may or may not be necessary. A scopalamine-morphine hypodermic injection will usually make the application painless and keep the patient comfortable. Under strict aseptic precautions, the cervix is gently dilated, sufficient to introduce the radium applicator. In most patients, especially in those over 35 years of age, a uterine curettage should be done and a specimen of the material perserved for microscopic examination. The length of the uterine canal should be determined by means of a sound, and the cross-arm rubber piece on the



Sketch of Radium Applicator.



Showing positions of Radium applicator and the vagina plugged with gauze.

applicator so adjusted, that when the Radium is in the body of the uterus, the cross arm-piece will fit snugly against the external os. A little K-Y jelly placed on the end of the applicator will facilitate ready insertion. Following the insertion of the applicator, the entire vagina, including the anterior and posterior fornix, is packed with gauze. This must be done carefully, the purpose being to keep the Radium in position in the uterus while holding the rectum and the bladder away. These latter parts are quite sensitive to radiation. If the packing is thoroughly done it requires about 10 yards of two-inch gauze.

The patient should be kept in bed the entire time the Radium is in the uterus. If unable to void urine, she should be catheterized every six hours. While the Radium is in situ some patients will complain of nausea and vomi-

ting. This, however, is usually not marked and disappears almost always with removal of the Radium. After removal of the Radium, the patient is placed in the Fowler position and permitted to be up the following day. A simple non-irritating, vaginal douche (daily) is advisable for about a month after the treatment.

One of the most important points in the treatment of uterine conditions with Radium is the proper dosage, especially in the initial treatment. This depends principally upon the age of the patient, except in malignant conditions, when large dosage is necessary regardless of age.

In patients above 35 years the usual dosage is 1200 mgm. hours (40 mgm. for 30 hours). This is considered a "sterilizing dose", and in the majority of patients, one such application will bring on the menopause with complete cessation of all uterine bleeding.

Uterine malignancies require still larger doses of Radium (2400 to 6000 mgm. hours) to control the disease.

All conditions of the cervix require a slightly different technique of applying the Radium than has been given above.

Most patients suffering from non-malignant uterine haemorrhage will be entirely relieved by one sterilizing dose of Radium. The haemorrhage may be relieved immediately, but more frequently it gradually diminishes and stops in about a month or two. A few patients report an execessive flow at the period following the application of the Radium, which is likely to happen if the Radium is applied just before the expected period. The ideal time for applying Radium is immediately upon the cessation of menstruation. If applied at this time, very frequently the patient never menstruates again if a sterilizing dose is administered. Since the results of Radium treatment may be prolonged, it is not advisable to give a second application until at least eight weeks have elapsed. When sterilizing doses are given, one or two menstrual periods may occur before complete amenorrhoea takes place. A watery discharge or persistent leukorrhoea may appear for some weeks after a large dosage of Radium. This is caused by the local reaction of the Radium, and gradually subsides. It is usually so insignificant that, unless the patient's attention is called to it, she makes no complaint. There is a gratifying sequel—a persistent leukorrhoea is frequently cured by the treatment.

About 50% of the patients suffering from non-malignant uterine haemorrhage will be relieved by one non-sterilizing dose of Radium (500 mgm. hours). The results are not so certain as when the larger Radium dosages are applied. The remainder of such patients will require two or more non-sterilizing doses of Radium, given at 2 or 3 monthly intervals, to successfully control the bleeding. The general post-menstrual history in these patients is that a period of amenorrhoea takes place, varying from two to three months, with ultimate reappearance of the normal flow. A few patients (about 20%) will fail completely to respond to small doses of Radium. In membranous dysmenorrhoea, puberty haemorrhages, and chronic cervicitis and endo-cervicitis (especially when leukorrhœa is the chief symptom) non-sterilising doses of Radium are indicated. Curtis reports 87% recoveries in patients with very persistent leukorrhœa. In endocervicitis intra-cervical application of Radium causes atrophy and obliteration of the glands, resulting in cessation of the discharge.

Lethal Cancer Dosage.—Wood and Prime, from animal experiments, expressed the belief that 4·5 to 7 E. D. of filtered X-rays or *gamma* rays are a lethal radiation tissue dose for rapidly growing, very cellular, and highly malignant tumours in man. But the lethal dose varies according to the location and histological character of the growth. Oral cancers require 2·5 E. D. for highly anaplastic growths, and about 10 E. D. for highly differentiated cancers. For uterine cancers 4 to 5 E. D. is considered lethal, and for breast cancers 10 to 12 E. D.

In cervical cancer the extent of growth is expressed in four clinical groups:

1. Clearly localised growth, on an average about 1 cm. diameter in all directions.

2. Doubtfully localised growth, characterised by an oedema or infiltration of the para-cervical connective tissue, and hence a decrease in the degree of downward displacement of the uterus.

3. The invasive growth, marked by definite invasion of parametria or regional lymph-nodes—but the invaded structures are movable, though mobility is decreased, due to loss of elasticity of the tissues of the parametrium.

4. The fixed and terminal growth, characterising the 'Frozen Pelvis'. It is distinguished by fixation of the tumour, due to invasion of the deep

visceral and parietal pelvic fasciae, or invasion of the vagina, urinary bladder or rectum, or the formation of distant metastasis.

An adequate tissue dose means a homogeneous impregnation, with a pre-determined radiation dose, of the entire true pelvis. The tumours of clinical groups 1, 2 and 3 are confined within the true pelvis. In all cancers judicious combination of Deep X-rays and Radium gives the best results. As the *gamma* rays from Radium are of shorter wave-length than 200 K. V. deep X-rays and more powerful, preference is given to preliminary X-ray radiation followed by radium application. Otherwise, the cells that have had the more powerful Radium rays, develop a degree of immunity against the weaker radiation from deep X-rays, and do not react equally favourably. Moreover, in the following groups the external radiation as the initial procedure is preferable. (1) In advanced lesions that have distorted the cervical canal, rendering it difficult and sometimes impossible to locate the external orifice. (2) In bulky papillary carcinomata which encroach upon and sometimes fill the vaginal cavity, rendering it impossible to insert the Radium into the vagina. (3) In patients with advanced lesions, marked weakness and secondary anaemia, in whom external radiation causes cessation of bleeding and improvement in general health. Under these conditions the Radium insertion is made 3 or 4 weeks after the external radiation, when the general condition of the patient is sufficiently improved to permit this procedure. In addition, pelvic infection, if any, will have cleared up. The whole procedure should have the object of giving an effective dosage (4 to 5 E. D.) in the true pelvis at the first instance. Deep X-rays through 4 or 6 fields in divided doses extending over a period of 2 to 3 weeks, saturating the pelvis with about 2 E. D., should be followed by Radium application to obtain the optimum dose. While the application of a single dose may vary from 2400 mgm. element hours to 3600 mgm. element hours, according to the extent of involvement, divided doses at intervals of a week may total 4800 to 6000 mgm. element hours in three equal doses. It is essential to complete the whole course in 2 to 3 weeks, as otherwise reaction of cancer cells to radiation will be less favourable, due to the development of radio-resistance. Within a radius of 3 cm. from the cervix, the combined X-ray and Radium dose will be around 4 to 5 E. D., and in the bony pelvic wall about 3 E. D. The treatment should be stopped if febrile symptoms arise. Severe anaemias with a red cell count below 3,000,000 per c. mm., and lecoupenia of below 4000 white cells per c. mm.

form definite contra-indications to radiation therapy. The general condition of the patient should be improved by adequate measures before radiation treatment is proceeded with.

The chief complications in the treatment by Radium are haemorrhage, bladder and rectal symptoms, and fistulae. If a sufficient dose is given to cure the carcinoma of the cervix, it will also be sufficient to produce an erythema in the rectum or bladder. This may be slight and clear up in a fortnight. If severe, rectal and bladder complications may develop 6 or 8 months after the initial irradiation. These late symptoms are frequently mistaken for recurrences, and additional radium treatment only causes more damage. If a fistula appears soon after treatment it is due to destruction from disease; if it appears late and there is no recurrence of carcinoma, it is probably due to progressive ulceration, or bladder or rectal complications, and hence a direct result of the treatment.

The distinctive and superior effect of Radium is the extension of differential killing effect to include cancer cells at the outermost margin of the growth. If we do not reach these outlying cells, our radium treatment has failed, except as a temporary palliative measure. The danger of recurrence lies in the deep cancer cells. Our real problem, as just stated, is to reach and devitalize these deep-lying cells. The best chance of doing this is by giving as large a dose as practicable of tbe deeply penetrating rays at the first application. This is accomplished by placing heavily screened Radium in the centre of the cancerous infiltration, and then packing the rectum and bladder as far away as possible so as to allow the maximum dose to act. Never again will conditions be as favourable for a devitalizing dose to the outlying cells as they are at the first application. If the opportunity is missed then it will not return.

GLEANINGS FROM MEDICAL LITERATURE

1 STATUS LYMPHATICUS

SYMMERS DOUGLAS

(*The American Journal of Surgery, Oct. 1934, Page 7.*)

Notwithstanding the recent conclusion of the British Commission that no such condition exists, most pathologists are convinced that 'Status Lymphaticus' presents definite anatomical features and that in it sudden death occurs with dramatic rapidity in apparently trivial circumstances and infections are ill-borne.

The association of sudden death with thymic enlargement was first noted by Bichat early in the 18th century. Paltauf and others showed that the persistent thymus was but one of a combination of hereditary anatomical imperfections. Dr. Charles Norris of the Bellevue Hospital, in 1905 and later, called attention to the importance of its clinical detection and its association with certain lesions of the ductless glands together with its occurrence in suicides and others of unstable emotional nature.

Status Lymphaticus may be defined as a combination of:

(1) hereditary constitutional anomalies associated with peculiarities of configuration ;

(2) preservation or even hyperplasia of the thymus and hyperplasia of the lymphoid tissues of the body;

(3) deficient genital development and altered distribution of hair;

(4) hypoplasia of the vascular system.

The condition is compatible with life, but is nevertheless a menace in that the instability of the lymphoid tissues provides a mechanism which is capable of so sensitising the body as to produce anaphylactic phenomena varying from urticarial rashes to convulsive seizures, asthmatic attacks, or sudden death. The same instability probably lowers the threshold of infection.

Clinical aspects.—Although clinical interest is focussed entirely on the fact that life may terminate abruptly on trivial provocation, the purpose here is to impress (1) the signs by which the condition may be detected ante-mortem; (2) the suggestive frequency of acute infection; (3) the disturbances of the nervous system and ductless glands; and,(4) the occurrence of cerebral haemorrhages in the young.

The clinical conglomerate of scrofula in the "angelic child" of the so-called lymphatic constitution and unusual susceptility to tuberculosis was long ago recognised by Gross (Sr); such are now known to be of the category of Status Lymphaticus.

After puberty, in the male, delicate texture of the skin, the well-nourished, often muscular, finely proportioned body, a feminine distribution of the pubic hair (i. e., not tending to grow upwards towards the umbilicus from the pubes), a smal penis and acorn-shaped glans, and scanty facial, axillary and thoracic hair make the clinical recognition easy. In the female, recognition is less easy, but an unusually delicate skin, an accentuation of the graceful outline of the body, and presence of small axillary pads are points to be noted.

The condition was noted in 6·2% of the autopsies at the Bellevue Hospital and was six times commoner in the male.

Etiology: Two *anatomical types,* one associated with unusually well marked changes in the lymphoid tissues, and another, the recessive type, marked by atrophic changes in the lymphoid structures, are recognised at autopsy.

In the well developed condition, the thymus is hyperplastic in every instance and the faucial, lingual and pharygeal tonsils in 50%. The follicles of the spleen and the intestine were hyperplastic in 88% of cases. A well-marked lymphocytosis in the peripheral blood is sometimes encountered.

In the majority of cases of the well developed condition and especially in subjects who have met with sudden death, the lymph nodes show a peculiar and characteristic change in the shape of the cells and the discharge of nuclear dust into the intercellular spaces.

Death in Status Lymphaticus is of the nature of an anaphylactic reaction, sensitisation being expressed in structural terms by the necrotic germinal follicles and chemically by the release of nucleo-proteids.

Cerebral Haemorrhage in the Young: The cerebral vessels, especially those forming the circle of Willis, show simple hypoplastic changes, a fact of profound importance from the standpoint of sudden death, since in such individuals a sudden increase of intracranial pressure, such as lifting heavy weights, straining at stool, tension of argument or fighting, may be disastrous. The medico-legal importance is obvious.

Emotional instability is frequently associated with status lymphaticus, while in such individuals associated exophthalmic goitre is common. There is also reason to believe that *chlorosis* is an incidental and fugitive condition in girls with status lymphaticus.

Though little is mentioned in the literature on the susceptibility of the subjects of status lymphaticus to infection, at autopsy on persons dying of diphtheria and cerebrospinal meningitis, the anatomical changes of status lymphatieus are to be seen in 25% of cases. M. K.

2 CARCINOMA OF THE MALE BREAST

GILBERT JUDSON

(*Surgery, Gynaecology and Obstetries, Oct. 1933. Page 451*)

The earliest reference to this condition is in the writings of Franciscus Arcaeus (1493—1573). The subject was first summarised in English literature by Williams (1894), and recently Wainwright (1927) made an extensive review of the subject.

Incidence: According to several authors the percentage varies from 0·86 to 8·4 of all breast cancers. The last figure is probably too high. Other figures given are 1·24% (Pack and Le Fevre), 1·5% (Deaver and McFarland), and 2% (Schuchardt).

Etiology. (a) *Heredity*: Appears to be secondary as a causative factor in male breast cancer.

(b) *Sex factor:* The inherent difference in the function of the gland is the most commonly accepted explanation of the relative rarity of cancer in the male as compared with the

female breast. This is also in accordance with the general rule that cancer seldom arises in vestigial structures.

(c) *Age incidence*: Cancer develops at a later period in males than in females, the average age being 54·4 years.

(d) *Side*: as in women there is a predominance of left-sided involvement.

(e) *Previous existence of benign tumours* have been noted, and chronic inflammatory lesions often precede the development of malignant disease; it is stressed that any small localised swelling of the male breast should be considered malignant until proved otherwise by microscopy. Disc or button shaped indurations beneath the nipple should be surgically removed at once.

(f) *Trauma* has been recorded as a possible etiological factor though there is much variance of opinion on its influence.

(g) *Gynaecomastia*: The association of gynaecomastia with male breast cancer, though observed, has not been sufficiently emphasized in the literature. Unusual development and activity of the breast are predisposing factors in cancer of the male breast.

The symptomatology, pathology, and distribution of metastases correspond to the well recognised manifestations of mammary cancer in general.

Treatment and end results: Cancer in the male breast should be treated on the same principles as in the female. Biopsies should be made if there is any uncertainty concerning the true nature of the disease. That these tumors are often small does not justify limited removal.

Irradiation is to be recommended as a valuable adjunct in inoperable cases; it is of great value in relieving the pain of bone metastases and in the treatment of local recurrences. Heavier doses by irradiation methods are recommended.

The prognosis of male mammary cancer is gloomy, though patients have lived for as long as 9 years after the first appearance of symptoms. These cases emphasize the necessity for frequent re-examination.

M. K.

3 A CASE OF EVIPAN PARALYSIS.

T. V. LANDER AND MAHOMED SALLAH

British Medical Journal, Nov. 24, 1934.

Chinese patient, aged 39, admitted on 5—2—34, with swelling, pain and redness in the region of the left knee of 4 days' duration, and surface appearances suggestive of cellulo-cutaneous erysipelas.

Operated upon on 8—2—34 under Evipan-Sodium without premedication. 9 cc. of the solution of 1 gm. of the drug in 10.5 cc. distilled water was administered, commencing at 11 a.m. Patient yawned at 2½ cc., and commenced to snore at 4 cc. Injection lasted 6 minutes. Operation commenced 11-10 a.m. and lasted 17 minutes, a large abscess cavity communicating with the joint being evacuated.

After operation, patient was breathing normally and moving his eyeballs, but did not recover full consciousness till 10-30 p.m.; strychnine 1/30 gr. and oxygen for half an hour was given at 3 p.m. Patient fully conscious next evening.

On 17—2—34, severe paralysis was noticed. The patient had been gravely ill meantime, due to the septic condition, and had not called attention to the paralysis. On interrogation he stated that it had been gradually coming on since operation but had not been present before.

Examination showed flaccid paralysis of both lower limbs, trunk and distal portions of the upper limbs, bilateral ankle and wrist drop. Knee, ankle and biceps jerks were absent, plantar reflexes flexor, abdominal cutaneous reflexes present, and there was no loss of control of sphincters. Sensibility to touch and pain diminished below the knees only. General wasting of muscles followed.

Treatment consisted of massage, rythmic interrupted sinusoidal current, iron and strychnine by mouth, flexion of wrists and ankles against resistance, and simple apparatus to prevent contractures.

Paralysis gradually improved, patient sat up early in April, walked slowly by middle of May, and recovery was practically complete by the 23rd of June; only the tendon reflexes were still negative and a slight left-sided foot-drop was present.

COMMENTARY.

The Manufactures claim absence of serious late consequences and no such cases have been recorded in the literature consulted by the writers, though they have noted early, evanescent toxic effects. The patient in question was admittedly gravely ill and emaciated before operation.

Willcox reports peripheral neuritis as one of the late toxic manifestations of the barbiturates and mentions toxic states as enhancing the susceptibility of patients to barbiturates.

The case was suggested to be one of acute beri-beri, but the prolonged unconsciousness after the injection and the great loss of power in the trunk muscles were against such an explanation.

M. K.

RURAL MEDICAL RELIEF

The reply of His Excellency Lord Erskine to the address presented at East Godaver was rather disappointing. We are not here concerned with the various other problems raised in the course of the addresses. But the statement that further extension of rural medical relief is to be postponed till the finances of the province improve is certainly most depressing! In spite of the many grievances of the rural practitioners and the frequent complaints of the rural authorities, it is generally admitted by all those who are familiar with the working of these institutions that the subsidized dispensaries play a very useful part in the scheme of medical relief in the province. It is the cheapest method of medical service to a community known in any country. The subsidy paid to the practitioners is certainly ungenerous. And if it were increased by fifty per cent or even a hundred per cent, we consider that it would still remain the cheapest form of agency for medical relief. While the demand for medical relief in the rural areas is insistent and increasing, the decision to cry halt to these institutions is certainly not wise. The argument of financial stringency may be very convenient for the Treasury Benches to silence adverse criticism. But it will not bear even a casual consideration.

It is common knowledge that times of financial distress produced by poor trade and unsuccessful agriculture are occasions for grave ill-health and virulent epidemics in the country. The aid of the medical man is required by communities more than ever under such conditions. Where for want of an organization or fore-thought medical relief is scarce in a country, when famine occurs, or epidemics break out, frantic efforts are made to make up for this neglect by hurriedly recruiting large numbers of medical men and by rushing up relief in various other directions. These emergency activites generally cost far more than a well regulated organization which has stood the test of time. Many epidemics are preventable. But in spite of all the recent knowledge and modern methods of prophylaxis, epidemics still occur, and sometimes they are of explosive virulence. The

prevailing storm of malaria in Ceylon is an instance of the kind. We are sure that if sufficient medical men have been available in the areas affected to treat the early cases efficiently, much of the appalling mortality would have been obviated. Similarly, epidemics of other diseases could be greatly minimised by prompt curative measures in the early stages. The sanitarian is certainly the most important person concerned in the maintenance of public health. But the need for medical men to look after the curative side of medicine is not less important. He supplements to a very large extent the usefulness of the sanitarian.

There is another aspect of this question of subsidized medical relief. Every year a large number of young men and women pass out of the medical schools and colleges. Apart from rendering medical relief to the rural areas, the creation of the rural dispensaries has been giving employment to a fair number of young doctors who would otherwise probably be unemployed. If, on account of poverty of funds, the State finds it difficult to employ larger number of medical men, the public would find it even more difficult to seek the aid of doctors on their own account. Thus, while sickness and death are likely to increase, the chances of a living for new medical men will greatly diminish. Such a state of affairs tends to prevent capable young men from joining the medical colleges and schools. Or, if, from excessive optimism they still seek medical education, it will end in a very large increase in the roll of the unemployed among the educated and cultured class. We are certain that the Government will not look on such a contigency with equanimity.

THE BUILDING CRAZE

Any organised scheme of medical relief to be effective requires accommodation to house the sick and men and materials to nurse them back to health. On this question there cannot be two opinions. But viewing the recent developments in the administration of the Medical Department, one is liable to entertain an honest doubt as to whether it concentrates all its resources on buildings. In the course of the last two years the accommodation side of the Presidency General Hospital has undergone a great change. A re-modelling scheme, providing for additions and alterations in abundance, has been pompously inaugurated, and the resultant conglomoration of edifices has received even gubernatorial blessing. More buildings are merrily springing up and the end of the scheme is not yet within sight. We do not cant at those institutions immortalizing the

memory of some whose sole claim for it seems to be that they drew their salaries in them. We have no quarrel with a building scheme as such. We admit that the more aesthetic among the public are finding a welcome change in the appearance of that mass of building situated in a busy part of the City. As the recent census figures reveal, the population of the City and the Presidency is steadily growing. As a natural corollary to this growth, a pro rata increase in the number of diseased persons at a particular time is also to be expected. The unprecedented and crushing economic depression is driving to the portals of the hospital a large mumber of people, who, under normal conditions, will resort to private medical relief. On the top of these, traffic accidents are also contributing their merry quota to the strength of the Hospital. Therefore, we do not desire to ignore the need for increased accommodation in a Presidency Hospital like the General Hospital. But what we are concerned with is the issue whether the building scheme is not occupying the attention of the authorities to the exclusion of all other matters and whether the resultant development is not an all too one-sided one. What is the use of a nice exterior if conditions whithin continue to remain stagnant? Are the patients, particulary poor patients, receiving that standard of treatment and conveniences which they reasonably expect in a popular institution of the type of the General Hospital? We are bound to point out that the complaints of the patients regarding both medical attention and comforts have not only not ceased but are ever on the increase. We dare say that, left to him, a sick man will rather prefer good treatment under a bad roof than indifferent treatment under a palatial roof.

While the building scheme swallows a decent portion of the resources at the disposal of the Government for medical relief, the lion's share of what is left is expended on the services, leaving but a pitiful moiety for expenditure on drugs and appliances. We have more than once urged in these columns (the columns of the *Bulletin*) the necessity for maintaining hospitals with a judicious mixture of paid and honorary staff. This Presidency is given credit for successfully working democratic institutions of a western origin. Then why, in the scheme of medical relief, western institutions should not be copied and why honoraries should not find an increasing place in hospitals pass our comprehension. Apart from that aspect of the question, we have here to draw the attention of the authorities to the fact that a well thought-out hospital plan should provide for simultaneous development of the structural and the curative side. It is, therefore, time for

the authorites to cry a halt to capital works and to turn their attention to hospital equipments and comforts of patients. The poor patient is crying for this change. Will his feeble voice be ever heard?

NEWS AND NOTES

OBITUARY

We regret to record the death, on January 27th, of Dr. A. R. Parasuram, T.D.D., M.R.C.P., Superintendent of the Tuberculosis Hospital and Director of the Tuberculosis Institute, Madras. He was aged only 47 at the time of his death. He leaves behind a widow and five sons and a large circle of friends and relations to mourn his loss.

It is our painful duty to record the death also of Dr. B. S. Mallayya, M.B., C.M., on January 29, at the age of 57, after a brief illness. He was a popular medical practitioner, and had taken a keen interest in politics and municipal problems for several years. He was recently elected to the Madras Legislative Council, of which he was a member for 3 years from 1926. He leaves behind him a widow, two sons and three daughters, and a large circle of friends and relations to mourn his loss.

MADRAS MEDICAL COUNCIL

Dr. U. Krishna Rau, M.B.B.S., has been returned unopposed to the Madras Medical Council to fill the vacancy caused by the death of Dr. M. S. Krishnamurthy Iyer, Dr. T. Satakopan, who also was standing for election, having withdrawn from the contest.

Dr. T. Satakopan, M.D., Physician, General Hospital, Madras, has been nominated a member of the Madras Medical Council to fill the vacancy caused by the death of Dr. T. Krishna Menon.

A MEDICAL MISCELLANY

The Trichinopoly District Medical Association is issuing a monthly *Miscellany* (from January 1935) for free distribution to its members. We have received a copy of the January number, which is admirably got up and contains an article on "Sterility, its causes and treatment", various useful extracts, and the transactions of the Association. We wish the *Miscellany* a useful and prosperous career.